# *IRE1 sulfenylation by reactive oxygen species coordinates cellular stress signaling*



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**IRE1 sulfenylation by reactive oxygen species coordinates cellular stress signaling**

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Maintenance of cellular homeostasis is a fundamental aspect of stress-responsive signal transduction pathways. Specific signaling pathways are often considered, and certainly most often studied, in the context of responses to a specific endogenous or environmental stressor, but there are also fundamental questions that remain regarding how information about stress pathways with potentially overlapping inputs and/or outputs is optimally integrated and transduced by the cellular circuitry. In the current issue of *Molecular Cell*, Hourihan et al. (this issue), combining molecular genetic and biochemical analysis in *Caenorhabditis elegans* and in mammalian cell systems, identify a mechanism by which IRE1, a principal regulator of the endoplasmic reticulum (ER) Unfolded Protein Response (UPR) (Ron and Walter 2011), also regulates a response to reactive oxygen species (ROS). Signaling through IRE1 to promote ER homeostasis and the response to oxidative stress appears to be mutually exclusive—that is, signaling one response turns off the other, and vice versa.

In a prior study, Blackwell and colleagues had carried out genetic studies that were suggestive of cross-regulatory interplay between SKN-1, the *C. elegans* homolog of the mammalian transcriptional regulator Nrf2, which regulates oxidative stress responses, and Unfolded Protein Response (Glover-Cutter et al., 2013). In the present study, Hourihan et al. nail down the underlying biochemical mechanisms, revealing an unanticipated post-translational modification of IRE1—sulfenylation, a reversible modification involving direct cysteine thiol group oxidation by reactive oxygen species to generate a sulfenic acid group. First, the authors show that IRE-1 is required for cellular responses to oxidative stress, including activation of the p38 mitogen-activated protein kinase (MAPK) pathway through the ASK1 MAPKKK. The authors show that pre-treatment with ER stress inhibits the response to

oxidative stress, and in turn, oxidative stress activation of IRE-1 inhibits the UPR. Second, the authors show that oxidative stress causes sulfenylation of IRE-1, specifically on C663, which activates the oxidative stress response and attenuates UPR signaling. That is, IRE-1 is a direct sensor of reactive oxygen species that can activate the SKN-1 pathway. Prior studies had shown that IRE1 associates with TRAF2 and ASK1 in mammals (Urano et al., 2000; Nishitoh et al., 2002), but here, the authors show that this association is required for downstream activation of p38 MAPK and SKN-1/Nrf2. The authors show that sulfenylation is not entirely necessary for the association with ASK1, but sulfenylation is required for the downstream phosphorylation of PMK-1/p38 MAPK and subsequent activation of SKN-1/Nrf2.

The susceptibility of the thiol group of cysteine to oxidation underlies its role in a number of bacterial and eukaryotic proteins that function in the detection of ROS and activation of homeostatic responses (D'Autréaux and Toledano, 2007). Recent proteomic studies have identified hundreds of sites of posttranslational modifications of cysteine residues in murine and human cells (Yang et al., 2014; Gould et al., 2015), but the functional significance of modified cysteine residues has awaited further characterization. The specific sulfenylation of C663 of IRE1 defined by Hourihan et al. has two distinct effects—IRE1 directly detects ROS, activating downstream SKN-1/Nrf2-dependent responses, and at the same time, the sulfenylation of this kinase active site cysteine effectively functions as a posttranslational modification to IRE1 that attenuates its activity in regulating the protein folding capacity of the ER. The aforementioned proteomic studies that have revealed a far greater prevalence of cysteine modification than previously appreciated (Yang et al., 2014; Gould et al., 2015) are particularly tantalizing in view of the detailed mechanistic validation of the effects of cysteine sulfenylation on signaling that has been carried out by Hourihan et al.

What might be the significance of IRE1 functioning as a signaling switch between the Unfolded Protein Response and the response to oxidative stress? The most familiar and common oxidation of the cysteine occurs during ERO1-catalyzed oxidative disulfide bond formation in protein folding in the ER, which generates hydrogen peroxide as a byproduct. Protein folding in the ER has been speculated to be a major endogenous contributor to cellular ROS (Tu and Weissman, 2004). Intriguingly, the major ER chaperone BiP, has also been shown to be regulated by sulfenylation, suggestive a functional coupling between the monitoring of oxidative stress and protein folding in the ER (Wang et al., 2014). The UPR responds to misfolded proteins in the ER by activating pathways that restore homeostasis, including the expansion of ER folding capacity (Ron and Walter, 2011). Perhaps sulfenylation of IRE1 by ROS not only activates antioxidant responses but also puts a brake on UPR activation, which might otherwise further increase levels of potentially damaging ROS through increased oxidative protein folding in the ER. The work of Hourihan et al. has opened the door to explore not only potentially wider roles for sulfenylation in eukaryotic signal transduction, but also to understand the how the maintenance of ER homeostasis is balanced with the challenges posed by generation of reactive oxygen species in the physiology of multicellular organisms.

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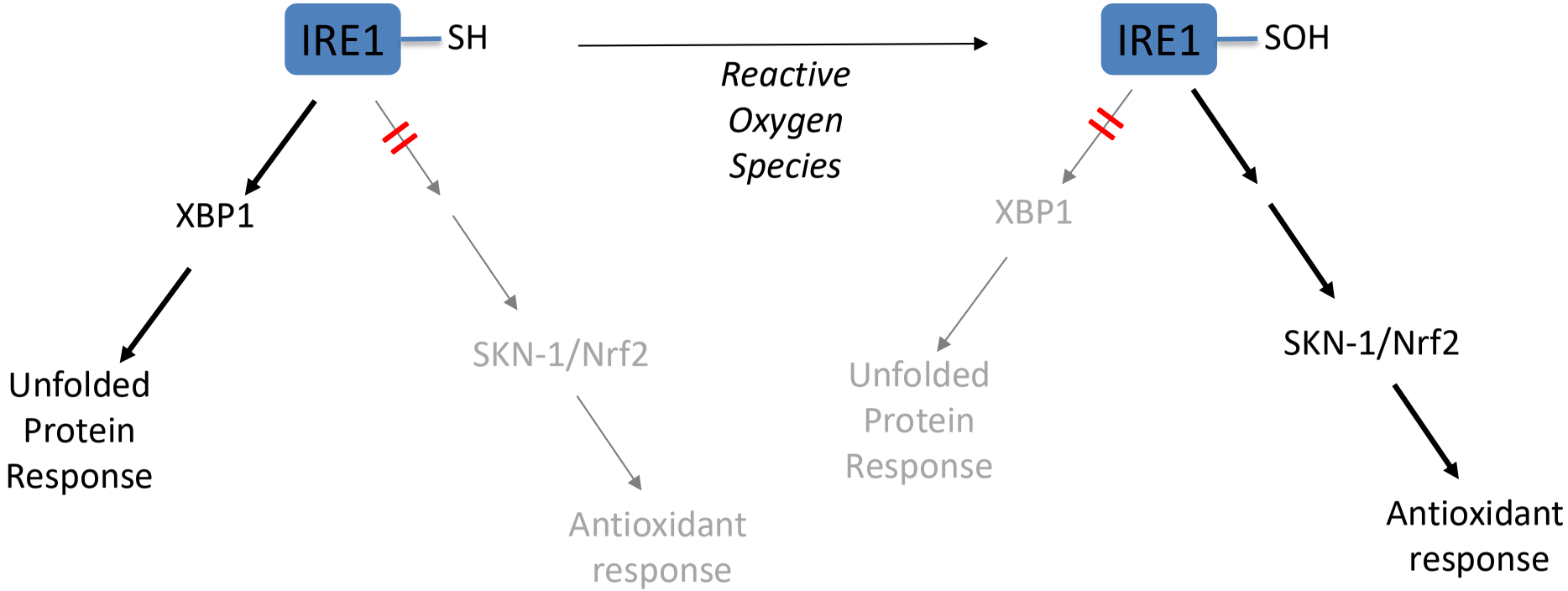


Figure 1. Sulfenylation of IRE1 by reactive oxygen species activates the SKN-1/Nrf2 oxidative stress response while attenuating UPR activation (Hourihan et al.).